REMARKS

Support for new claim 117 is found on page 2, lines 10-14 and 22-23, and page 96, lines 16-18.

Rejections under 35 USC§112

The Examiner has cited additional references which touch on the difficulty in treating cancer yet still has not presented any evidence which remotely suggests the methods claimed herein are not enabled. In addition, the Examiner has not presented any evidence to refute the disclosure within the specification or the findings and conclusions made in the numerous publications cited in the application that raf inhibition has been correlated with the inhibition of growth of a variety of tumor types. In the absence of such evidence, the rejection is deficient under controlling case law. The burden is upon the Patent and Trademark Office to provide evidence shedding doubt that the invention can not be made and used as stated; see for example, *In re Marzocchi*, 439, F. 2d 220, 169 USPQ 367 (CCPA 1971). As a matter of Patent Office practice then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to that used in describing and defining the subject mater sought to be patented must be in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for the enabling support. See, *In re Marzocchi*, *supra.* The evidence and reasoning presented by the Examiner has no relevance as to whether the data, disclosure and assertions in Applicant's disclosure are

inaccurate. The Examiner continues to rely on general statements and conclusions which are unsupported, outdated and ambiguous. For example, the Examiner states:

> No compound has ever been found to treat solid tumors, carcinomas, myeloid disorders or adenomas of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a 'silver bullet' is contrary to our present understanding of oncology.

No evidence has been presented to support these statements. In fact, a search for issued U.S. patents with claims to the treatment of carcinomas, myeloid disorders and adenomas uncovered the following:

7,056,944
6,914,066
6,905,669
6,861,445
6,784,195
6,706,711
6,699,865
6,696,458
6,593,357
6,528,509
6,495,582
6,169,096
6,037,350

In addition, a search for US patents which claim a single agent or a combination of agents for treating solid tumors uncovered numerous patents, of which five recent patents are listed below:

U.S. Patent 7,091,226 (epothilone B)

U.S. Patent 7,087,627 (tubulin binding agent plus inhibitor of formation of Nitric Oxide)

U.S. Patent 7,041,301 (α-interferon)

U.S. Patent 6,995,164 (Taurolidine, Taurultum or derivatives thereof)

U.S. Patent 6,992,106 (Stilbine derivatives)

The Examiner relies on the Cecil Textbook of Medicine and cites the following language therein , "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study." This statement provides no indication that a single agent would not be effective against multiple disorders or, more particularly solid tumors, carcinomas, myeloid disorders or adenomas. The statement suggests variations in the treatment of different cancers are necessary but there is no indication that these treatments can not comprise a common feature such as treatment with a common agent.

The Examiner continues to rely on *In re Buting,* 163 USPQ 689 (CCPA 1969) citing the statement "evidence involving the single compound and two types of cancer, was held insufficient to establish the utility of the claims directly to disperate types of cancers." No evidence has been presented that this statement made over 35 years ago reflects the state of the art today. In fact, this statement is inconsistent with the claims in the recently issued patents identified above.

The Examiner cites Stein as representative of the state of the prior art and quotes the following statements:

> a physicians approach to the treatment of patients with cancer varies depending on the following features organ of origin, histology and stage, paraneoplastic syndromes, age of the patient and the presence of other morbid diseases.

and

> Cancer represents hundreds of other diseases with many causes. Although each disease may share certain general features with others, the approach to therapy for a give[n] problem will vary.

These teachings by Stein do not preclude the treatment of multiple diseases with a single agent. There is no indication that the variation and the approach to therapy requires different agents be employed or that a single agent will not be effective. The variation in therapy referred to by Stein appears to be that of a skilled physician in treating a particular patient and such variation is routine (frequency of size of dose, administration of other drugs, radiation, etc.).

The Examiner's analysis of the claimed subject matter under the factors set forth in *In re Wands*, 8 USPQ 2d 1400 and *Ex Parte Foreman*, 230 USPQ 546 is also flawed. As discussed above, the Examiner's reliance on statements made 35 years ago in *In re Buting,* is not a proper analysis of the state of the prior art. The Examiner also has not provided a proper assessment of the predictability or lack thereof in the art , the amount of directional or guidance present, the presence or absence of working examples, the breadth of the claims or the quantity of experimentation needed.

As to "predictability", the two compounds employed in the methods of this invention are exemplified in the specification (see entries 42 and 43, and page 66, lines 4-13) and tested for raf kinase activity in the *in vitro* assay described on pages 94 and 95. No evidence has been presented that these assays are insufficient to establish the activity of the recited compounds as raf kinase inhibitors. At the time of Applicant's invention, the inhibition of raf kinase had

already been correlated with the inhibition of the growth of a variety of tumor types (see Monia et al.). The inhibition of raf expression had also already been correlated with the blocking of cell proliferation (Kloch et al.) and the reversion of transformed cells to the normal growth phenotype type (Daum et al., Fridman et al.). No evidence has been presented to refute the findings of conclusions made in these publications. While "pharmacological activity in general may be very unpredictable," no evidence has been presented that the raf kinase assay selected is inaccurate or insufficient to predict pharmacological activity. The Examiner recites *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970), for the holding, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." However, there is no evidence that the assays employed are not highly predictive of pharmacological activity so the findings in Fisher provide no basis to restrict the scope of the claims herein.

Applicants clearly provide sufficient guidance to make and use the invention. As discussed above, the synthesis of the two recited compounds is described on page 66. Methods for preparing pharmaceutical compositions with these compounds and methods for administering compounds in the treatment of cancers are provided on pages 10-14. Contrary to the Examiner's assertions, dosages are provided on page 13, lines 11-20. To the extent the disclosure does not provide specific dosages, it would at most involve routine experimentation, if any at all, for one skilled in the art to treat any one of the recited cancers with the compounds of this invention. The enablement requirement is satisfied if, "the specification teaches those in the art enough that they can make and use the claimed invention without "undue experimentation" See, *Amgen Inc. v. Hoechst Marion Roussel,* 314 F.2d 1313, 65 USPQ 2nd 1385 (Fed Cir. 2003). Using the

claimed compounds would be routine for those skilled in the art in view of Applicant's disclosure.

The Examiner also alleges that "there is no demonstrated correlation that the tests and results apply to all of the disorders embraced by the instant claims." Correlation of raf kinase inhibition with the treatment of various cancers was known in the art as discussed in the Background of the Invention and the reference made to Monia et al. on page 96, lines 16-18 of the specification. Explicitly providing dedicated assays for each form of cancer is not necessary to enable a method claimed. See for example, *In re Howarth* 654 F.2d. 105, 210 USPQ 689 (CCPA 1981) "an inventor need not explain every detail since he is speaking to those skilled in the art". *In re Gay,* 309 F.2d.749, 774, 135 USPQ 311 (CCPA 1962) "not every last detail is to be described or else patent specifications would turn into production specifications which they were never intended to be". There is no requirement that Applicant provide any working examples relating to the treatment of every claimed disease to satisfy the statute. See for example, *In re Angstadt and Griffin,* 537 F.2d. 502, 190 USPQ 214 (CCPA 1976). In Angstadt it was decided an Applicant is not required to disclose "every species encompassed by the claims even in an unpredictable art." The Federal Circuit held in *Utter v. Higarn,* 845 F.2d. 998, 6 USPQ 2d 1714 (1988), that a specification may, within the meaning of §112, 1st paragraph, enable a broader claimed invention without describing all species that the claim encompasses. It is noted that the MPEP also sets forth a policy which does not mandate such examples and states that, compliance with the enabling requirement of 35 U.S.C. §112, first paragraph, "does not turn on whether an example is disclosed."

The Examiner has not provided an appropriate analysis of the scope of the claims in rejecting all claims under 35 U.S.C. §112, first paragraph. The Examiner has collectively analyzed all claims as having similar scope and has assumed the claims embrace the treatment of all types of solid tumors, carcinomas, myeloid disorders and adenomas. However, many claims are directed to specific carcinomas (e.g., claims 87 and 108), specific myeloid disorders (e.g., claim 93 and 109), specific carcinomas (e.g., claims 100-104), Due to their varying scope, the claims herein require separate treatment for the analysis under 35 U.S.C. §112, first paragraph.

The Examiner alleges the quantity of experimentation would be an undue burden to one skilled in the art. The Examiner cites a Medline Abstract by Crump for the following quote, "Adult acute myeloid leukemia (AML) and the myelodysplastic syndromes (MDS) remain a formidable therapeutic challenge." This statement provides no indication or insight that the methods provided herein require any experimentation, let alone undue experimentation in treating such disorders, The specification provides more than it needs to in form of assays and IC_{50} values. In a similar fashion, one of ordinary skill in the art by performing the same or similar tests can by routine experimentation determine the activity levels of each of the claimed compounds in treating various cancers. This is absolutely routine in the field. This is true for either known cancers and those that may be discovered in the future.

Basically, the Examiner is relying on papers concerned with whether the FDA will or will not approve a drug for use against multiple cancers. But this is irrelevant to utility and enablement for patent purposes. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

For the reasons indicated above, Applicants maintain that they have provided more than adequate guidance and examples to enable the claimed invention and submit all claims meet the requirements of 35 U.S.C. §112, first and second paragraphs.

Double Patenting:

Applicants maintain the provisional obvious-type double patenting rejections are premature in that allowed subject matter has not been identified in the co-pending applications identified. If these rejections were the only outstanding rejections, Applicants submit that these rejections should be withdrawn.

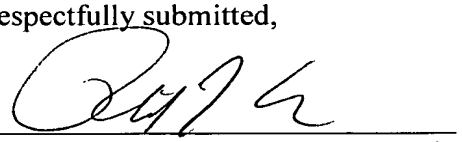
International Publication WO00/420132:

WO 00/420132 and the above-identified application presently name the same inventive entity. However, with the last amendment restricting the list of claims to two compounds, Mary-Katherine Monahan, Joel Renick and Robert Sibley are no longer inventors and the PCT publication, WO 00/420132, is a publication by "another" under 35 U.S.C. §102(a). However this PCT publication provides no prior art effect under 35 U.S.C. §102(a) because to the extent the PCT document discloses the narrower subject matter now claimed herein having a smaller inventive entity, this constitutes a disclosure not more than one year before the effective filing date of this application. This would not constitute a prior art event. *In re Katz* 687 F2d 450 215 USPQ 14 (CCPA 1980). Under the same rationale, the PCT publication and any subsequent U.S. patents issuing therefrom, cannot be references under 35 U.S.C. §102 (e) against this application under the Katz rationale. Moreover, 35 USC §§ 102(e) /103 would also not apply because, at all times, the subject matter of the PCT document and that of this application was commonly owned(35 USC 103(c) In view of the above remarks,

favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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